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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WILDER, CYNTHIA B	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 04/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/631,613	HOGREFE ET AL.	
	Examiner	Art Unit	
	Cynthia B. Wilder, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-44,69,70,72 and 74* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-44,69,70,72 and 74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 9/9/1998 is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed on March 15, 2004. The indicated finality of claims 40-44, 69-70, 72, 74 is withdrawn in view of new ground(s) of rejection. Claims 1-39, 45-68, 71, 73, 75-94 are canceled. Claims 40-44, 69-70, 72, 74 are pending.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 40-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of enhancing a nucleic acid polymerase comprising mixing a nucleic acid template for the DNA polymerase with at least one nucleic acid polymerase, wherein said nucleic acid polymerase is Pfu DNA polymerase and adding a polymerase enhancing composition comprising at least one component of extracts of *pyrococcus furiosus (*Pfu) species possessing polymerase enhancing activity, or Pfu protein possessing polymerase enhancing activity, such as e.g. Pfu P50 protein or Pfu P45 protein or P300 protein complex from *pyrococcus furiosus*, or cell extracts, protein and protein complexes possessing polymerase enhancing activity from other archeabacterial sources, such as e.g., *Thermococcus*, or dUTPase possessing polymerase enhancing activity from archeabacterial or eukaryotic sources, it does not reasonably provide enablement for a method of enhancing a nucleic acid polymerase reaction comprising, mixing a nucleic acid sequence template for a nucleic acid polymerase with at least one nucleic acid polymerase and adding any isolated or purified naturally occurring protein,

possessing polymerase enhancing activity obtained from any bacterial, eukaryotic or archeabacterial source or any wholly or partially synthetic protein having the same amino acid sequence as the naturally occurring protein or analogs thereof, protein complexes of one or more of the naturally occurring proteins, or wholly or partially synthetic proteins and partially purified cell extracts containing one or more of the naturally occurring proteins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The first paragraph of section 112 requires the specification describe how to make and use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue (See In re Wands, 858 F. 2d 731, 8 USPQ2d 1400, 1404, (Fed. Cir. 1988)). These factors include, but are not limited to:

I. Quantity of Experimentation Necessary

The claimed invention is drawn to a method of enhancing any of the numerous nucleic acid polymerases by mixing a nucleic acid sequence template for a nucleic acid polymerase with at least one nucleic acid polymerase and adding a polymerase enhancing composition comprising at least one component possessing nucleic acid polymerase enhancing activity selected from: an isolated or purified naturally occurring protein, possessing polymerase enhancing activity, obtained from a bacterial, eukaryotic or archeabacterial source; a wholly or partially synthetic protein having the same amino acid sequence as the naturally occurring protein or analogs thereof, possessing polymerase enhancing activity; polymerase-enhancing mixtures of one or more of the naturally occurring proteins, or wholly or partially synthetic proteins; polymerase

enhancing complexes or one or more of the naturally occurring proteins, or wholly or synthetic proteins; and polymerase-enhancing partially purified extracts containing one or more of the naturally occurring proteins. This claims as written are directed to a method which encompasses any and all nucleic acid polymerases and any and every possible extract, protein, protein complex, mixtures of proteins and analogs thereof in a process for enhancing polymerase activity.

The specification at page 5 defines "a polymerase enhancing activity" as the ability to increase the rate, fidelity and/or yield of a nucleic acid polymerization reaction mediated by a nucleic acid polymerase, or to expand or alter the range of conditions under which such reaction does or may proceed. The specification broadly teaches that the term "polymerase enhancing factor (PEF)" includes purified naturally occurring polymerase enhancing factors and wholly or partially synthetic copies or active analogs thereof.

In the Summary of the Invention and Detailed Description beginning at page 5, the specification discloses that extracts of *Pfu* cells are provided that enhance the activity of *Pfu* DNA polymerase as well as human dUTPase, which enhances polymerase activity. Further the specification teaches that PEF complexes such as e.g., the P300 complex from Pfu cells sample extracts, which comprises protein components namely the P50 protein and P45 protein, function to enhance the activity of polymerase. Likewise the specification discloses that other Pfu proteins having molecule weight between 42 and 60 kD alone or in combination functions to enhance polymerase activity. The examples beginning at page 20 discloses wherein polymerase enhancing factor (PEF) activity was screened in Pfu DSM 3638 cells, identified, purified or partially purified and tested for polymerase enhancing factor in replication reactions,

amplification reactions, cloning and mutagenesis assays. The specification however does not teach or describe a method of enhancing any of the numerous nucleic acid polymerases by mixing a nucleic acid sequence template for a nucleic acid polymerase with at least one nucleic acid polymerase and adding a polymerase enhancing composition comprising at least one component possessing nucleic acid polymerase enhancing activity selected from: an isolated or purified naturally occurring protein, possessing polymerase enhancing activity, obtained from a bacterial, eukaryotic or archeabacterial source; a wholly or partially synthetic protein having the same amino acid sequence as the naturally occurring protein or analogs thereof, possessing polymerase enhancing activity; polymerase-enhancing mixtures of one or more of the naturally occurring proteins, or wholly or partially synthetic proteins; polymerase enhancing complexes or one or more of the naturally occurring proteins, or wholly or synthetic proteins; and polymerase-enhancing partially purified extracts containing one or more of the naturally occurring proteins. The specification does not disclose or describe the unlimited extracts, proteins and analogs that are encompassed by the invention as claimed. Likewise, the specification does not provide a definition of a polymerase enhancing composition commensurate in scope with the claims as written. In fact, the specification only provides working examples and discussion for extracts of *Pyrococcus furiosus* cells, proteins isolated from *Pyrococcus furiosus* cells, polymerase enhancing complex (P300 complex) comprising proteins components (P45 and P50) isolated from *Pyrococcus furiosus* as functioning to enhance the activity of Pfu DNA polymerase. Additionally the specification asserts that the addition of human, *Pyrococcus furiosus* and *Thermus thermophilis* dUTPase enhances polymerization reactions. Nowhere in the specification is there a disclosure wherein the unlimited number of extracts, proteins, complexes,

mixtures or analogs thereof as encompassed by the claimed invention are functional in enhancing polymerization reactions. Likewise there is no indication from the specification that any of the numerous other nucleic acid polymerase known in the art, such as e.g., Kornberg polymerase, Klenow fragment, T4 DNA polymerase, T7 DNA polymerase, Taq DNA polymerase, Micrococcal DNA polymerase, Alpha DNA polymerase, *Ecoli* RNA polymerase, SP6 RNA polymerase, T3 RNA polymerase, T7 RNA polymerase, RNA polymerase II, Poly(A) polymerase, exo-Vent polymerase and/or etc., are indeed enhanced when in the presence of the unknown, unlimited extracts, proteins, complexes, mixtures or analogs encompassed by the claims as written. The specification provides no information to allow one of ordinary skill in the art to make or use the claimed method using the large number of undisclosed proteins, extracts, analogs, proteins complexes, mixtures or analogs thereof that are encompassed by the claims. As to the quantity of experimentation required, one of skill in the art would have to design an experimental procedure to detect and screen for agents that possess polymerase enhancing activity that is commensurate with the entire scope of the claims. Undue burden would be required of the practitioner as the invention encompasses a plethora of unknown protein species and numerous nucleic acid polymerases.

II. Amount of Direction and Guidance and Presence and absence of Working examples

The specification does not provide a method of enhancing a nucleic acid polymerase reaction by mixing a nucleic acid sequence template for a nucleic acid polymerase with at least one nucleic acid polymerase and a polymerase enhancing composition that bears a reasonable correlation to the entire scope of the claims. The examples beginning at 20 to page 68 lack information concerning using a polymerase enhancing composition comprising any and every

possible extract, protein, protein complex, mixtures or analogs thereof. There is no guidance in the specification for detecting any and every possible extract, protein, complex, mixture of proteins or analogs thereof which may or may not be functional to enhance a polymerization reaction. Without undue experimentation, one of ordinary skill in the art would not recognize which proteins, extracts, mixtures, complexes or analogs thereof possess polymerase enhancing activity. As noted earlier, the specification only discloses, extracts from Pfu cells as possessing Pfu DNA polymerase enhancing activity, proteins comprising molecular weight of 42-60 kD alone or in combination as possessing Pfu polymerase enhancing activity, protein complex P300 comprising protein components (P45 and P50) as possessing Pfu polymerase enhancing activity. Additionally the specification asserts that dUTPase from bacteria or eukaryotic cells possess polymerase-enhancing activity. Since the specification only provides limited polymerase enhancing factors which functions to increase the rate, fidelity and/or yield of a nucleic acid polymerization reaction, it would be impossible to predict with certainty the effect of the numerous other proteins, extracts, mixtures, complexes or analogs thereof on enhancing polymerization in a reaction. Merely making reference that the present invention comprises extracts, protein complexes, and related proteins that possess PEF derived from organisms other than Pfu as being encompassed by the invention does not enable the practitioner to reproduce the results reported in the specification for the broad scope of the claims.

III. Level of predictability or unpredictability in the art

a. The specification has not enabled a method of enhancing a nucleic acid polymerase reaction that is commensurate fully in scope. While the molecular biology techniques utilized are know in the art, it is not routine in the art to screen multitudes of

proteins, extracts, mixtures of proteins, protein complexes or analogs thereof to determine nucleic acid polymerase enhancing activity. Additionally, the results of any screening or modification thereof is unpredictable since a reasonable expectation of success is limited by a lack of knowledge concerning the functionally of all of the possible proteins, extracts, protein mixtures, protein complexes or analogs thereof claimed by the invention. Therefore without sufficient knowledge and guidance, determining a polymerase enhancing composition as claimed is unpredictable and the experimentation left to those in the art is unnecessarily and improperly extensive and undue. Thus, for all of the foregoing reasons, undue experimentation is necessary for one of skill in the art to obtain the claimed invention.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 69-70, 72 and 74 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claim 69-70 are indefinite because the claims do not recite a final process step that clearly relates back to the preamble. The claims are drawn to "a method of enhancing a nucleic acid polymerase reaction. However, the claims only recites a step of "adding a P45 protein..". Thus it cannot be determined if the goal of the preamble is achieved or not and if achieved, in what step it is achieved. While minute details are not required in method claims, at least the basic

steps must be recited in a positive, active fashion (see *ex parte Erlich*, 3 UsPQ2d1011, p.1011 (Bd. Pat, Applicant. Int.1986).

(b) Claims 69-70, 72 and 74 are indefinite for the recitation of PEF because abbreviations often have more than one meaning in the art. It is suggested inserting the full name of the abbreviation as supported by the specification as originally filed into the claims for clarity.

(c) Claims 72 and 74 are indefinite because the claims do not recite a final process step that clearly relates back to the preamble. The claims are drawn to "a method of controlling the activity of a polymerase in a polymerization reaction". However, the claims only recites a step of " changing the amount of dUTP present or generated..". Thus it cannot be determined if the goal of the preamble is achieved or not and if achieved, in what step it is achieved. While minute details are not required in method claims, at least the basic steps must be recited in a positive, active fashion (see *ex parte Erlich*, 3 UsPQ2d1011, p.1011 (Bd. Pat, Applicant. Int.1986).

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an

international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

6. Claims 40-44 rejected under 35 U.S.C. 102(a) and 35 U.S.C. 102(e) as being anticipated by Nielson et al (US 5605824, publication date: February 25, 1997; effective filing date October 24, 1990). Regarding claim 40, Nielson et al. disclose a method of enhancing a nucleic acid polymerase reaction comprising (a) mixing a nucleic acid sequence template with a nucleic acid polymerase and adding a polymerase enhancing composition comprising an isolated protein possessing polymerase enhancing activity (col. 2, lines 49-52, 58-66, col. 3, lines 44-64 and Figure 2; see also col. 7, lines 23-43).

Regarding claim 41, Nielson et al. disclose an embodiment of claim 40, wherein the reaction is a replication reaction (col. 2, lines 63-65).

Regarding claim 42-43, Nielson et al disclose an embodiment of claim 40, wherein said reaction comprises an amplification reaction, such as e.g., PCR (col. 3, lines 44-64 and Figure 2).

Regarding claim 44, Nielson et al. disclose an embodiment of claim 42, further comprising cloning or sequencing process as applicable by the method (col. 16, lines 31-41). Therefore, Nielson et al. meets the limitations of the claims of 40-44 of the instant invention.

Conclusion

7. No claims are allowed. However, Claims 69, 70, 72 and 74 are free of the prior art.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia B. Wilder, Ph.D. whose telephone number is (571) 272-

0791. The examiner works a flexible schedule and can be reached by phone and voice mail. Alternatively, a request for a return telephone call may be emailed to cynthia.wilder@uspto.gov. Since email communications may not be secure, it is suggested that information in such request be limited to name, phone number, and the best time to return the call.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Cynthia Wilder

CYNTHIA WILDER
PATENT EXAMINER

4/9/2004